ORIGINAL RESEARCH

Simultaneous administration of high-dose atorvastatin and clopidogrel does not interfere with platelet inhibition during percutaneous coronary intervention

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Background: Reloading with high-dose atorvastatin shortly before percutaneous coronary interventions (PCIs) has been proposed as a strategy to reduce periprocedural myonecrosis. There has been a concern that statins that are metabolized by cytochrome P450 3A4 may interfere with clopidogrel metabolism at high doses. The impact of simultaneous administration of high doses of atorvastatin and clopidogrel on the efficacy of platelet inhibition has not been established.

Methods: Subjects (n=60) were randomized to receive atorvastatin 80 mg together with clopidogrel 600 mg loading dose (n=28) versus clopidogrel 600 mg alone (n=32) at the time of PCI. Platelet aggregation was measured at baseline, 4 hours after clopidogrel loading dose, and 16–24 hours after clopidogrel loading dose by light transmittance aggregometry using adenosine diphosphate as agonist.

Results: Platelet aggregation was similar at baseline in both the atorvastatin and the control groups (adenosine diphosphate 10 µM: 57%±19% vs 61%±21%; P=0.52). There was no significant difference in platelet aggregation between the atorvastatin and the control groups at 4 hours (37%±18% vs 39%±21%; P=0.72) and 16–24 hours post-clopidogrel loading dose (35%±17% vs 37%±18%; P=0.75). No significant difference in incidence of periprocedural myonecrosis was observed between the atorvastatin and control groups (odds ratio: 1.02; 95% confidence interval 0.37–2.8).

Conclusion: High-dose atorvastatin given simultaneously with clopidogrel loading dose at the time of PCI does not significantly alter platelet inhibition by clopidogrel. Statin reloading with high doses of atorvastatin at the time of PCI appears to be safe without adverse effects on platelet inhibition by clopidogrel (ClinicalTrials.gov: NCT00979940).

Keywords: clopidogrel, atorvastatin, myocardial infarction, percutaneous coronary intervention, platelet aggregation

Introduction

High-dose statin therapy has been well established in the medical therapy of acute coronary syndromes (ACS) and in secondary prevention of cardiovascular disease. Beyond the low-density lipoprotein lowering and high-density lipoprotein raising properties, pleiotropic off-target effects of statins have been invoked in the dramatic reduction of thrombotic cardiovascular events. In the PROVE-IT TIMI 22 trial, intensive therapy with atorvastatin 80 mg daily was superior to pravastatin 40 mg daily in reducing ischemic events after ACS with a 16% relative risk reduction for a composite end point of death, myocardial infarction, documented unstable angina requiring hospitalization, revascularization,

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and stroke in the atorvastatin group.[1] Similarly, others have investigated the beneficial properties of pretreatment with statins prior to elective percutaneous revascularization. A meta-analysis including nine trials documented an odds ratio of 0.45 for the occurrence of periprocedural myonecrosis in patients treated with statins prior to coronary intervention.[2] Whereas earlier studies included patients who were pretreated with statins for at least 2 days prior to percutaneous coronary intervention (PCI), more recent trials have suggested that shorter pretreatment with statins may provide similar protection.[3,4] In the NAPLES II study, atorvastatin 80 mg administered 24 hours prior to PCI significantly reduced the incidence of myocardial infarction in statin-naïve patients.[4] Similarly, in the ARMYDA-RECAPTURE study, reloading with atorvastatin 80 mg 12 hours prior to PCI and 40 mg immediately pre-PCI in patients on chronic statin therapy reduced the 30-day major adverse cardiovascular event rate from 9.4% to 3.7% (P=0.037).[5]

Clopidogrel is a prodrug that requires metabolism by the hepatic cytochrome P450 (CYP) system (2C19, 1A2, 2B6, 3A4, 3A5, and 2C9 isoforms) to provide an active metabolite.[6] It has been shown that inhibition of CYP metabolic capacity such as in the case of CYP2C19 by omeprazole and other proton pump inhibitors can lead to inadequate clopidogrel metabolite formation and reduced platelet inhibition. High residual platelet reactivity during treatment with clopidogrel is associated with significantly increased risk for adverse ischemic events after PCI.[7]

Due to the common CYP3A4 pathway shared by many of the statins (simvastatin, atorvastatin, lovastatin) and clopidogrel, there has been a concern for clinically significant interactions. A documented interaction between atorvastatin and clopidogrel was first described in 2003 by Lau et al,[8] but other studies have not been able to confirm this effect using other platelet-testing modalities during maintenance therapy.[9,10] Analysis of data from the CHARISMA trial studying 10,078 patients with statin therapy at baseline randomized to dual therapy with clopidogrel and aspirin versus aspirin alone did not demonstrate an effect of CYP3A4-metabolized versus non-CYP3A4-metabolized statins on clinical end points.[11] In clinical practice, administration of maintenance statin and antiplatelet agents is often separate, with the former generally being prescribed in the evening and the latter in the morning. However, as early upstream administration of high-dose atorvastatin is being increasingly adopted for patients admitted with ACS, concomitant administration with clopidogrel is more likely to occur. No study has so far investigated the effects of simultaneous administration of high-dose atorvastatin (80 mg) with high loading dose clopidogrel (600 mg) on early platelet inhibition post-PCI.

Methods
Study design and patient population
The ESTATE study (effects of short term, high-dose aorvastatin therapy on periprocedural myonecrosis and platelet inhibition after PCI) is a randomized open-label pilot study to evaluate the effects of high-dose atorvastatin loading immediately before PCI on periprocedural myonecrosis and platelet inhibition. The study was approved by the Indiana University institutional review board. Written informed consent was obtained from all subjects. Subjects were eligible to be enrolled in the study if they were found to have significant coronary artery disease (CAD) with angiographic stenosis of ≥70% in one or more coronary arteries and were undergoing PCI for stable CAD. Patients undergoing catheterization for ST-elevation myocardial infarction (MI), non-ST elevation MI, or high-risk unstable angina were not enrolled in the study. Exclusion criteria included age >85 years and <21 years, recent myocardial infarction within the last month, cancer, renal failure with creatinine >3.0 mg/dL, liver cirrhosis, lymphoproliferative disorder, pregnancy, thrombocytopenia <150,000/mm^3, coagulopathy (international normalized ratio [INR] >1.5), abnormal liver function tests, illicit drug use, history of statin intolerance, history of rhabdomyolysis, and planned use of glycoprotein IIb/IIIa inhibitors during PCI. Given that only very few patients who were referred for cardiac catheterization were statin naïve, we allowed subjects who had received simvastatin (which was the primary statin prescribed in our institution) to be enrolled if last simvastatin dose was administered at least 1 day prior. Subjects treated with atorvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin were excluded from participation. All patients received aspirin 81–325 mg orally prior to diagnostic catheterization.

Patients were randomized 1:1 to receive either atorvastatin 80 mg orally or no additional atorvastatin, along with standard clopidogrel 600 mg loading dose immediately prior to beginning of ad hoc PCI in the catheterization laboratory. Randomization occurred by opening of previously prepared sealed envelopes containing random allocation. The original sample size of the study (n=88) was calculated based on power 0.8 (two-sided alpha of 0.05) to detect the relative reduction in risk of periprocedural myonecrosis previously demonstrated in a study of moderate-dose atorvastatin pretreatment for several days before PCI.[3] The study was stopped after 60 subjects due to slower than expected enrollment.

Blood samples

Blood samples were taken from arterial sheaths in the catheterization laboratory before administration of clopidogrel and atorvastatin. Follow-up blood samples were obtained by venipuncture 4 hours and 16–24 hours after loading dose of clopidogrel. All blood samples were directly transferred into vacutainer tubes containing Na citrate 3.2% and analyzed within 2 hours. Light transmittance aggregometry was performed with a Chronolog 700 aggregometer in platelet-rich plasma using platelet poor plasma as reference as previously described.[12,13] Adenosine diphosphate (ADP) at 5 μM, 10 μM, and 20 μM was used as agonist. Platelet inhibition was defined as % change in platelet aggregation from baseline in subjects not on baseline clopidogrel. Cardiac troponin I and creatinine kinase-MB (CK-MB) were measured 8 hours and 16 hours after PCI.

End points

Periprocedural myonecrosis was defined as a rise in cardiac troponin I above the upper limit of normal (ULN) for the assay at any time point after PCI. Periprocedural myocardial infarction was defined as postprocedural rise in CK-MB >3× ULN.[14]

Statistics

Statistical analysis was performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA). Statistical significance was defined as $P<0.05$. Two-sided tests were conducted, and the values are represented as mean ± standard deviation except as otherwise stated. Categorical variables were compared using the χ^2-test. Normal distribution of continuous data was assessed by the Kolmogorov–Smirnov test. Unpaired two-sided Student's t-test was used to compare normally distributed continuous data between the two groups. Multivariable linear regression analysis was performed using on-treatment platelet aggregation as dependent variable to evaluate the effects of assigned treatment arm with forward stepwise adjustment for baseline clinical variables, as well as adjustment for prior treatment with simvastatin and clopidogrel.

Results

Sixty patients who were undergoing elective PCI were randomized to receive either atorvastatin 80 mg together with clopidogrel 600 mg loading dose (n=28) or clopidogrel 600 mg alone (n=32).

Table 1 Baseline demographics and clinical variables

Variables	Atorvastatin (n=28)	Control (n=32)	P-value
Age (years)	62.6±10	61.4±8	0.6
Weight (kg)	97.9±32	103.7±48	0.58
Male sex (%)	22/28 (79%)	25/32 (78%)	0.97
Race			0.33
Caucasian (%)	22/28 (79%)	29/32 (91%)	
African American (%)	5/28 (18%)	3/32 (9.4%)	
Asian (%)	1/28 (4%)	0/32 (0%)	
Prior CAD (%)	17/28 (61%)	22/32 (69%)	0.52
Congestive heart failure (%)	4/28 (14%)	5/32 (16%)	0.89
Diabetes mellitus (%)	13/28 (46%)	14/32 (44%)	0.84
Hypertension (%)	27/28 (96%)	30/31 (97%)	0.92
Hyperlipidemia (%)	25/28 (89%)	29/32 (91%)	0.86
Current smoking (%)	11/28 (39%)	10/32 (31%)	0.66
Baseline clopidogrel use (%)	7/28 (25%)	6/32 (19%)	0.56
Daily aspirin dose			0.6
81 mg	11/28 (39%)	12/32 (38%)	
162 mg	0/28 (0%)	1/32 (3%)	
325 mg	17/28 (61%)	9/32 (59%)	
Prior treatment with simvastatin (%)	21/28 (75%)	22/32 (69%)	0.59
Proton pump inhibitor (%)	10/28 (36%)	13/32 (41%)	0.63
ACE inhibitors (%)	17/28 (61%)	20/32 (63%)	0.76
Beta blockers (%)	26/28 (93%)	26/32 (81%)	0.29
Calcium channel blockers (%)	6/28 (21%)	5/32 (16%)	0.6
Coronary artery intervention			
Left anterior descending artery	9/28 (32%)	11/32 (34%)	0.86
Circumflex artery	8/28 (29%)	11/32 (34%)	0.63
Right coronary artery	14/28 (50%)	13/32 (41%)	0.47
Number of stents implanted	1.48±1.2	1.58±0.8	0.71

Notes: Data presented as mean ± standard deviation unless otherwise stated. Comparison of variables with Student's t-test for continuous variables and χ^2 for categorical variables.
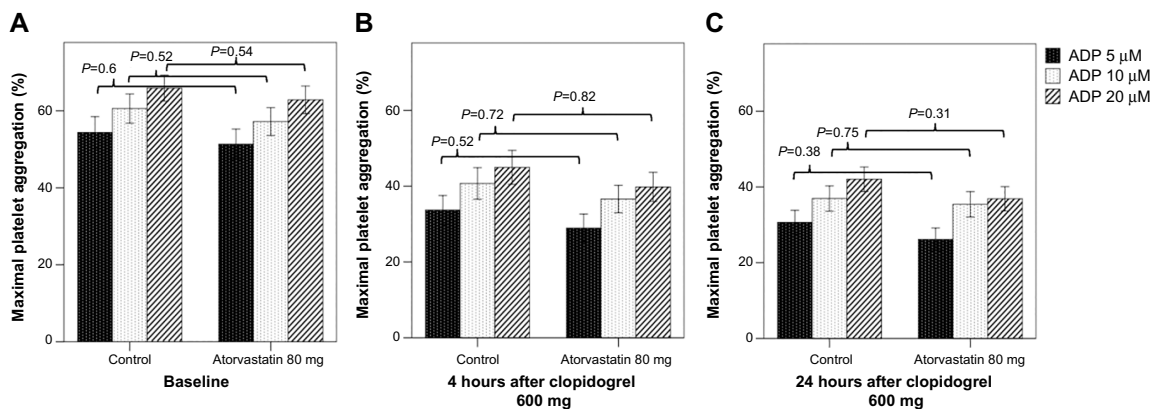**Abbreviations:** CAD, coronary artery disease; ACE, angiotensin-converting enzyme.

Figure 1 Platelet aggregation.
Note: Maximal platelet aggregation measured at baseline (**A**), 4 hours (**B**), and 24 hours (**C**) after clopidogrel loading dose administration.
Abbreviation: ADP, adenosine diphosphate.

One patient in the control (no atorvastatin) group received abciximab during the procedure at the discretion of the operator and was excluded from the analysis in the platelet substudy. Clinical variables of the subjects enrolled in the study are delineated in Table 1. There were no significant differences in the prevalence of clinical variables among groups. An average of 1.53 stents were implanted during the PCI, with 91% being drug-eluting stents. The target vessel was the left anterior descending artery in 33%, the circumflex artery in 32%, and the right coronary artery in 45% of cases.

At baseline prior to clopidogrel and atorvastatin administration, there was no significant difference in baseline platelet aggregation induced by ADP (Figure 1A). Platelet aggregation decreased at 4 hours after clopidogrel administration in both the atorvastatin and the control groups, with only minimal additional decrease in maximal platelet aggregation for all agonists studied at 16–24 hours (Figures 1B and C). There was a nonsignificant trend toward lower on-treatment maximal platelet aggregation in the atorvastatin group as compared to the control group at both time points. Similarly, there was no significant difference in platelet inhibition between the atorvastatin and control groups (Figures 2A and B). Multivariable linear regression analysis demonstrated no

significant association between atorvastatin treatment arm and final on-treatment platelet aggregation after adjustment for clinical variables and pretreatment with clopidogrel or simvastatin (Table 2).

As previously reported by other investigators, a large number of subjects with uncomplicated PCI demonstrated periprocedural myonecrosis, as defined by elevation in cardiac troponin I above the ULN (Figure 2C). A smaller fraction of subjects demonstrated a rise in CK-MB above the ULN (Figure 2C). For both measures, no difference in incidence of periprocedural myonecrosis was observed between atorvastatin and control groups (troponin >1× ULN: odds ratio: 1.02; 95% confidence interval [CI] 0.37–2.8; P=0.97; CK-MB >1× ULN: odds ratio: 0.84; 95% CI 0.17–4.1; P=0.83). Two subjects in the atorvastatin group and one subject in the control group had a periprocedural myocardial infarction as defined by CK-MB rise above 3× ULN (odds ratio: 2.4; 95% CI 0.2–28; P=0.5).

Discussion

The results of our study suggest that simultaneous administration of high-dose atorvastatin 80 mg and clopidogrel 600 mg loading doses does not significantly increase the risk
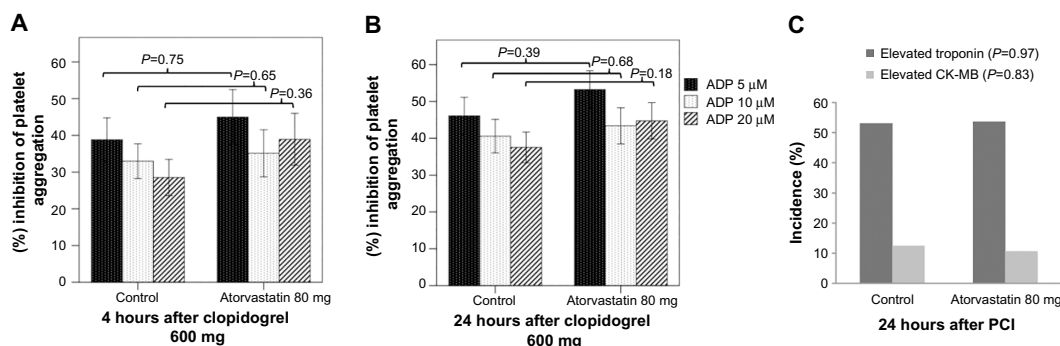

Figure 2 Platelet inhibition 4 hours (**A**) and 24 hours (**B**) after clopidogrel loading dose. Periprocedural myonecrosis after PCI (**C**).
Abbreviations: ADP, adenosine diphosphate; CK-MB, creatinine kinase-MB; PCI, percutaneous coronary intervention.

Table 2 Multivariable analysis of atorvastatin treatment with forward stepwise adjustment for baseline clinical variables and baseline clopidogrel and simvastatin treatment

Dependent variable: maximal platelet aggregation at 16–24 hours	B-value	95% Confidence interval	P-value
ADP 5 µM	−2.6	−11.2 to 5.9	0.54
ADP 10 µM	−0.7	−10.7 to 9.3	0.89
ADP 20 µM	−4.0	−13 to 5.1	0.39

Abbreviation: ADP, adenosine diphosphate.

of high posttreatment platelet reactivity. While our study was not powered to demonstrate effectiveness in reducing the risk of periprocedural myocardial necrosis, given early termination of the study prior to targeted enrollment, and its pilot design, there was no difference in rates of periprocedural myonecrosis between subjects with and without concomitant high-dose atorvastatin administration. Previous studies by other investigators have suggested that high-dose atorvastatin given within a short time interval of 12 hours before PCI in patients with ACS may significantly reduce the risk of major cardiac events. In addition, updated guidelines recommend atorvastatin 40–80 mg/d or rosuvastatin 20–40 mg/d for secondary prevention of CAD.[15] Thus, high doses of atorvastatin are increasingly being coprescribed in patients undergoing ad hoc PCI who may be started on clopidogrel concomitantly during an admission for an ACS. Many studies have evaluated the pharmacodynamic interactions of CYP3A4-metabolized statins and clopidogrel, with the majority evaluating the effects of chronic statin exposure on platelet reactivity.[8–11,16–22] The timing of peak hepatic plasma exposure to the parent drugs may affect the extent of the pharmacodynamic interaction. The majority of studies examining statin–clopidogrel interaction have used traditional timing of dose administration, with statins being prescribed in the evening and antiplatelet agents in the morning. This may significantly influence the degree of interaction given that atorvastatin has a terminal half-life of ~10 hours.[23] The majority of studies have demonstrated no consistent effect of atorvastatin treatment on clopidogrel response or clinical event rates, with few exceptions. Leoncini et al[24] demonstrated improved platelet inhibition among patients randomized to high-dose atorvastatin who were previously found to have high platelet reactivity on clopidogrel. Some studies have suggested a modest pleiotropic anti-aggregatory effect of low-dose atorvastatin with reduction of ADP platelet reactivity after treatment for several months as well as improvement in prevalence of aspirin resistance, which could in part counterbalance a reduction in clopidogrel platelet inhibition.[25,26] In contrast,

Park et al[18] showed that changing atorvastatin to a non-3A4-metabolized statin significantly improved platelet inhibition among nonresponders to clopidogrel with high posttreatment platelet reactivity. Pelliccia et al[27] recently reported that treatment with low-dose atorvastatin was associated with a small but significant increase in platelet reactivity among patients treated with clopidogrel, but this effect was only observed in subjects with high baseline on-treatment platelet reactivity by Verify Now assay. These conflicting results suggest that among certain individuals, in particular subjects who have high residual platelet reactivity during treatment with clopidogrel, concomitant treatment with high-dose atorvastatin could contribute to differences in pharmacodynamic response to clopidogrel. However, the results of this study suggest that simultaneous administration of high-dose atorvastatin and clopidogrel loading dose does not significantly impair early platelet inhibition after PCI, which is supported by lack of differences in outcomes among patients with statins in large clinical trials of clopidogrel.[11,28,29]

Limitations of this study include the open-label study design and that not all patients were naïve to statins and clopidogrel at the time of enrollment. Also, no other platelet agonists were studied other than ADP. Additional limitations are the relatively small sample size and the premature termination of the study after slow enrollment, leading to decrease in power to detect significant differences in incidence of periprocedural myonecrosis.

Conclusion

The results of our study indicate that simultaneous administration of high-dose atorvastatin and clopidogrel prior to PCI appears to be safe and does not significantly alter platelet inhibition by clopidogrel.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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